

# The pivotal role of PFO in paradoxical embolism following venous sclerotherapy: a unique case report with pathological correlations

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## Background

Vein sclerosing therapy for varicose veins remains an extremely popular procedure. Cerebrovascular accidents can be a serious complication. A patent foramen ovale (PFO) can act as a conduit to the arterial circulation, which could explain the adverse neurologic consequence of this procedure. This case provides pathologic evidence of this concept.

## Case summary

A 66-year-old female presented with syncope after undergoing varicose vein sclerotherapy. A computed tomography angiography of the head and neck in the emergency room revealed an occluded right distal M1 middle cerebral artery. Clot retrieval was performed with final pathology revealing amorphous material consistent with an exogenous agent, polydocanol foam, which was used for the patient's vein sclerotherapy. A transthoracic echocardiogram and transoesophageal echocardiogram showed a PFO, which was ultimately closed percutaneously.

## Discussion

In a quarter of the population, lack of closure of the intrauterine interatrial shunt leads to the existence of a PFO. This direct communication between the atria provides an anatomical conduit for paradoxical emboli and eventually infarction of affected tissues. While a paradoxical embolism is an uncommon cause of acute arterial occlusion, it can have catastrophic sequelae. Historically, the presence of an arterial thrombus from the venous circulation has been difficult to establish unless the thrombus is visualized in transit through a PFO. Complications from vein sclerotherapy have been reported in the literature and include transient ischaemic attacks and strokes, however, this is the first case to provide pathological proof of a paradoxical embolism, which ultimately resulted in percutaneous closure of the PFO.

## Keywords

Case report • Patent foramen ovale • Percutaneous closure • Stroke • Paradoxical embolism • Syncope • Cerebrovascular accident

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## Learning points

- Patent foramen ovale (PFO) should be considered in patients with new stroke and recent venous thrombi.
- There can be limited evidence of paradoxical emboli. When able, any thrombus retrieved from a stroke thrombectomy should be sent for pathology if there is suspicion for paradoxical embolism in a recent venous procedure using exogenous material.
- Percutaneous closure of a PFO should be considered in patients with proof of paradoxical embolism.

## Introduction

Vein sclerosing therapy is an extremely popular procedure in the management of varicose veins. However, it comes with potential serious risks including cerebrovascular accidents (CVAs) and transient ischaemic attacks (TIA). The likelihood of these complications occurring hinges on the presence of a patent foramen ovale (PFO), a persistent embryologic right to left shunt that acts as a conduit for paradoxical emboli.

## Timeline

Day 0	Patient undergoes vein sclerosing therapy procedure
Day 0–3.5 h after procedure	Development of left-sided weakness prompts ED visit. Computed tomography angiography head revealed occluded right distal M1 middle cerebral artery
Day 0–3 h after arrival to ED	Undergoes urgent neurovascular thrombectomy; final pathology consistent with polidocanol foam
Day 2	Transthoracic echocardiogram reveals patent foramen ovale (PFO)
Day 61	Undergoes transoesophageal echocardiogram for further evaluation of PFO
Day 418 (1 year and 1 month after stroke)	PFO closure with NobleStitch™ EL device

## Case presentation

A 66-year-old white female presenting with a history of headache, blurred vision, and syncope 3.5 h after undergoing varicose vein sclerosing therapy. At presentation to the emergency department (ED), she was haemodynamically stable. A neurologic exam revealed a flaccid left upper extremity, increased tone of the left lower extremity, and left-sided hemi-neglect. Her cardiovascular exam revealed a regular rhythm with a heart rate of 81 b.p.m.; no murmurs were present. An electrocardiogram was normal sinus rhythm with occasional premature ventricular contractions.

The patient reported a past medical history of thyroid cancer and osteoporosis. Levothyroxine was her only home medication. She was a non-smoker and drank alcohol twice weekly. At the time of presentation, the differential diagnosis included acute ischaemic or haemorrhagic CVA, atypical migraine, hypertensive encephalopathy, hypoglycaemia, or electrolyte abnormalities. Labs from the emergency room revealed a normal comprehensive metabolic panel, complete blood count, and coagulation labs. A high sensitivity troponin level was 10 ng/L (normal <14 ng/L).

She underwent computed tomography angiography of the head and neck, which revealed an occluded right distal M1 middle cerebral

artery (MCA) and limited flow in the M2 superior division (*Figure 1*). The contents of the occlusions were thought to be air and thrombus. She was immediately taken for endovascular intervention. Clot retrieval in the distal right M1 MCA was performed. Final pathology revealed laminated blood consistent with a thromboembolism. The retrieved clot contained amorphous material composed of an exogenous agent. This was consistent with the polidocanol foam, which was used during her vein sclerosing procedure (*Figure 2*). As part of her stroke work-up, a transthoracic echocardiogram (TTE) and transoesophageal echocardiogram were performed and she was found to have a PFO.

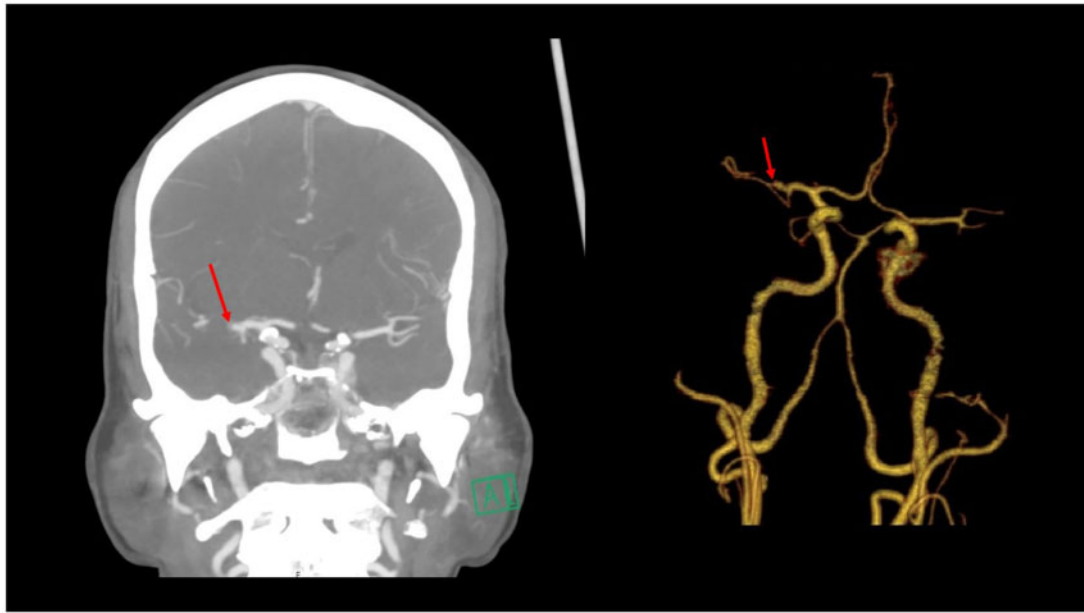
The decision was made to perform percutaneous closure of the patient's PFO. A diagnostic right heart catheterization was initially performed showing an oxygen saturation of 70% at the superior vena

cava and 70% oxygen saturation at the main pulmonary artery (PA). The calculated Qp:Qs was 1, indicating no shunt. Right-sided pressures, PA pressure, pulmonary capillary wedge pressure, and left atrial pressures were normal (*Table 1*). Intra-cardiac echocardiogram (ICE) showed the known PFO with right to left-right shunt throughout the cardiac cycle (*Video 1*). A NobleStitch™ EL device (HeartStitch, Fountain Valley, CA, USA) was used to close the PFO (*Video 2*). Repeat ICE and bubble study showed no residual shunt (*Video 3*).

The patient was seen for outpatient follow-up at 34 and 219 days post-procedure. A follow-up TTE at 209 days revealed a small residual interatrial shunt, significantly improved from baseline. She reported doing well with no further neurologic symptoms suggest of stroke or TIA after undergoing intense physical therapy. She will remain on low-dose aspirin indefinitely.

## Discussion

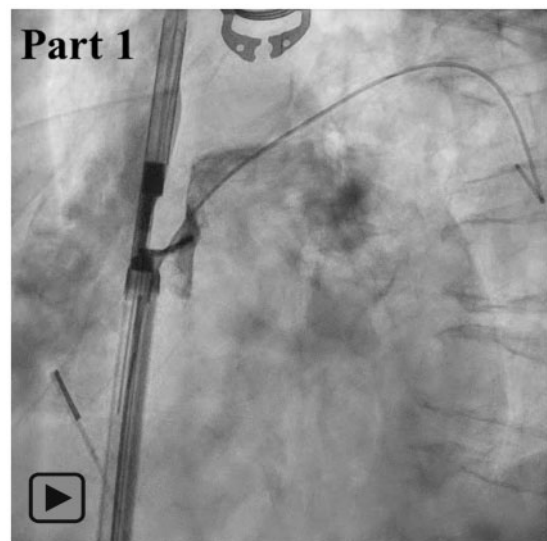
During foetal development, blood from the placenta returns to the right atrium to be shunted through a passageway between the atria known as the foramen ovale. This right-left interatrial shunt forms at



**Figure 1** Computed tomography angiography of the head showing distal occlusion (red arrows) of the right M1 middle cerebral artery at the level of the bifurcation.



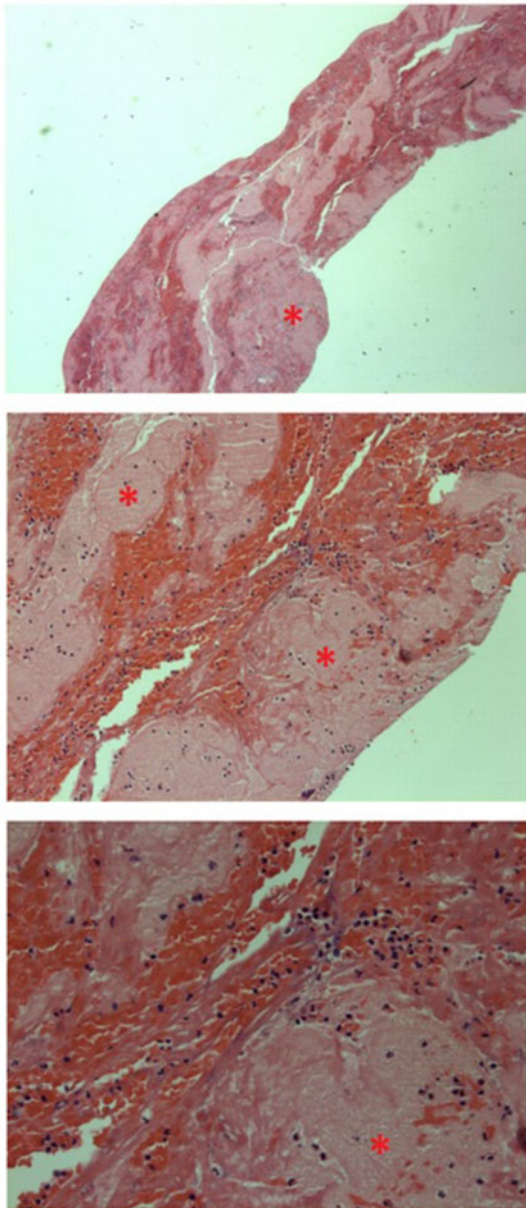
**Video 1** Intra-cardiac echocardiogram showing the patent foramen ovale. There is a right-to-left shunt as shown by colour Doppler.



**Video 2** Cine fluoroscopy of patent foramen ovale closure using NobleStitch™ EL. (Part 1) The device is situated in the fossa ovalis and engages the septum secundum. The needle passes through the septum secundum, capturing the suture. (Part 2) The suture-carrying arm of the device is now drawn against the septum primum. The needle is advanced to pick up the suture.

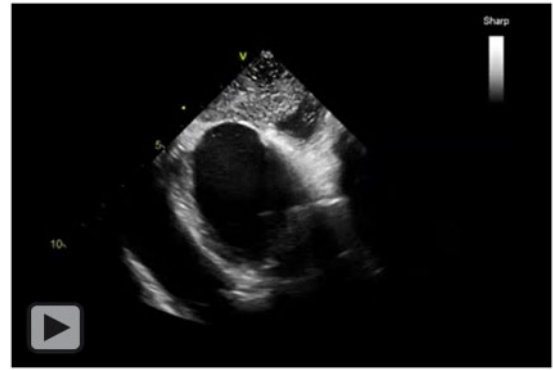
the fourth week of development and is one of two intrauterine shunts that allows passage of oxygenated blood to the systemic circulation, bypassing the foetal lungs. Postnatally, when the lungs become functional, the pulmonary vascular pressure decreases and the left atrial pressure exceeds that of the right, forcing the closure of the septum primum and septum secundum. Functional closure begins at the first breath and is rapid; however, anatomical closure is much slower and occurs before the end of the first year. In 25% of the population, lack of closure leads to the existence of a PFO. This direct communication between the right and left-sided circulation via a PFO can serve as a passageway for paradoxical embolization.

Approximately 31% of the 800 000 strokes that occur in the USA every year are labelled cryptogenic and in 40% of these patients, a PFO is present.<sup>1</sup> Mechanistically, a paradoxical embolism starts with the formation of a deep vein thrombosis (DVT). Once it propagates



**Figure 2** Thrombus retrieved from right middle cerebral artery showing the aspirated material. The clotted material contains laminated blood consistent with thromboembolus and amorphous material (red asterisk) consistent with an exogenous substance.

and dislodges, the thrombus can enter the right atrium where a transient increase in right atrial pressure can cause movement through a PFO and into the left atrium. From there, it can travel to the left ventricle and out through the aorta where it can occlude coronary, cerebral, renal, mesenteric, or peripheral arteries. This occlusion can lead to eventual infarction of affected tissues and, depending on the location, can clinically manifest itself as neurological deficits, chest pain, abdominal pain, or a cold limb.<sup>2</sup> A paradoxical embolism is an uncommon cause of acute arterial occlusion, but it can have catastrophic



**Video 3** Intra-cardiac echocardiogram showing small residual right to left shunt by bubble study.

**Table 1** Haemodynamic pressures obtained prior to patent foramen ovale closure

Right atrial pressure (mmHg)	8/8/7
Right ventricular pressure (mmHg)	24/2/9
Main pulmonary artery pressure (mmHg)	24/8/15
Pulmonary capillary wedge pressure (mmHg)	12
Left atrial pressure (mmHg)	13/11/8
Left ventricular end diastolic pressure (mmHg)	12

sequelae and the presence of a PFO should be considered in all patients with an arterial embolus.

It is extremely difficult to establish the presence of an arterial thrombus from a DVT and/or a thrombus in transit through a PFO.<sup>3-5</sup> Without the direct visualization of an entrapped thrombus within the defect, it can only be assumed that the cause could be a paradoxical embolus. In our patient's case, evidence of this concept came from the agent used during the vein sclerosing procedure. Polidocanol, also known as laurmacrogol 400, is a surfactant micro-foam used frequently during vein sclerotherapy. It acts as a detergent and disrupts endothelial cells by dissolving essential molecules from the membrane surface. When injected intravenously to a varicose vein, polidocanol destroys the vessel walls causing aggregation of platelets, cellular debris, and fibrin. Systemic adverse events and complications following sclerotherapy have been documented in the literature, including CVAs and TIA. In 2011, Sarvananthan et al.<sup>6</sup> published a review of 41 studies that included a total of 10 819 patients who underwent sclerotherapy. Twelve cases of CVA with confirmed head imaging were reported and 97 cases reported various other neurologic manifestations, including visual and speech disturbances and migraines. Eleven patients were found to have a right to left cardiac shunt, but no cases reported pathological proof of the embolus. In our patient's case, the aspirated clot from the MCA contained an amorphous exogenous material consistent with polidocanol foam. To the best of our knowledge, this is the first case to provide pathological proof of a paradoxical embolism.

After closure of the PFO, the patient underwent routine monitoring of access sites and was discharged the following day on aspirin 81 mg daily and clopidogrel 75 mg daily for 6 months. She has had no other neurologic sequelae and a follow-up TTE showed no residual shunting.

## Conclusion

While the concept of a PFO as a conduit for paradoxical emboli has been described in the literature and in reports of neurologic complications from vein sclerotherapy, the evidence has been shown mainly from imaging. Because of the retrieved clot, we are able to provide microscopic evidence of exogenous material that followed the pathway from venous to arterial occlusion via a PFO. This proof of concept provides pathological confirmation of the role of PFO in paradoxical embolism.

## Lead author biography



Eileen C. Gajo was born in Chicago, Illinois, and raised in Los Angeles, California. She graduated from the University of California Irvine with a degree in biological sciences. She went on to pursue her doctor of medicine degree at the Ross University School of Medicine and completed a residency in internal medicine at the University of Chicago (NorthShore). After serving a chief resident year, she became board certified in internal medicine

and is currently completing her fellowship in general cardiology at the Rush University Medical Center where she will also complete her interventional cardiology fellowship.

## Supplementary material

[Supplementary material](#) is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.

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